# PATENT COOPERATION TREATY

# PCT



## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

**(PCT Article 36 and Rule 70)**

| Applicant's or agent's file reference<br>5119-11101 | **FOR FURTHER ACTION** | See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) |
|---|---|---|
| International application No.<br>PCT/US03/23131 | International filing date *(day/month/year)*<br>24 July 2003 (24.07.2003) | Priority date *(day/month/year)*<br>24 July 2002 (24.07.2002) |
| International Patent Classification (IPC) or national classification and IPC<br>IPC(7): C12Q 1/24; C12M 1/34 and US Cl.: 435/30, 287.1 | | |
| Applicant<br>BOARD OF REGENTS, THE UNIVERSITY OF TEXAS SYSTEM | | |

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 7 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of report with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

| Date of submission of the demand | Date of completion of this report |
|---|---|
| 17 September 2003 (17.09.2003) | 03 May 2004 (03.05.2004) |
| Name and mailing address of the IPEA/US<br>Mail Stop PCT, Attn: IPEA/US<br>Commissioner for Patents<br>P.O. Box 1450<br>Alexandria, Virginia 22313-1450<br>Facsimile No. (703) 305-3230 | Authorized officer<br>William H. Beisner<br>Telephone No. 571-272-1700 |

Form PCT/IPEA/409 (cover sheet)(July 1998)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US03/23131

## I. Basis of the report

1. With regard to the **elements** of the international application:*

☐ the international application as originally filed.

☒ the description:
pages 1-12, 14-44, 50 as originally filed
pages NONE, filed with the demand
pages 13 and 45-49, filed with the letter of 30 October 2003 (30.10.2003)

☒ the claims:
pages 51-60, as originally filed
pages NONE, as amended (together with any statement) under Article 19
pages 61, filed with the demand
pages NONE, filed with the letter of _____.

☒ the drawings:
pages 1-14, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☐ the sequence listing part of the description:
pages NONE, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination(under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in printed form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☒ The amendments have resulted in the cancellation of:

☐ the description, pages NONE

☒ the claims, Nos. 73

☐ the drawings, sheets/~~fig~~ NONE

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*
*** Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US03/23131

**V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. STATEMENT

| | | | |
|---|---|---|---|
| Novelty (N) | Claims | 31-55,62,63,65-71 | YES |
| | Claims | 1-30, 56-61, 64, 72 | NO |
| Inventive Step (IS) | Claims | 50-55, 69 | YES |
| | Claims | 1-49, 56-68, 70-72 | NO |
| Industrial Applicability (IA) | Claims | 1-72 | YES |
| | Claims | NONE | NO |

2. CITATIONS AND EXPLANATIONS

Please See Continuation Sheet

**Supplemental Box**
(To be used when the space in any of the preceding boxes is not sufficient)

Claims 1-30 and 72 lack novelty under PCT Article 33(2) as being anticipated by Rotman. The reference of Rotman discloses an analyte detection system that includes a body (10); a porous membrane (22 or 24); a top member (12) which is transparent to light (See Figure 4).); a cavity (48) formed between the top member and the membrane and a bottom member (14).

Claims 56-61 and 64 lack novelty under PCT Article 33(2) as being anticipated by Freiburghaus et al. The reference of Freibrughaue et al. discloses an analyte detection particle that includes a receptor and a plurality of pores that have a diameter of less than 1micron (See pages 5-6).

Claims 1-17, 19-21 and 72 lack novelty under PCT Article 33(2) as being anticipated by Poitras. The reference of Poitra discloses an analyte detection system that includes a body (10); a porous membrane (26); a top member (16) which is transparent to light (see column 2, lines 40-52); a cavity formed between the top member and the membrane and a bottom member (12).

Claims 1-49 lack an inventive step under PCT Article 33(3) as being obvious over Weinreb et al. The reference of Weinreb et al. discloses an analyte detection system and method of use that includes a body for supporting a porous membrane. Fluid can flow across the membrane and through the membrane (See Figures 11 and 23). While the device includes the structural elements for flowing an analyte with respect to the membrane to capture a desired analyte and optically image the captured analyte, the reference is silent as to the use of a transparent cover member. However, in view of the fact that the material captured in the openings of the membrane are intended to be optically imaged, it would have been obvious to one of ordinary skill in the art to provide the device with a cover member for the known and expected results of preventing contamination of the contents of the membrane holder. The use of a transparent cover would allow optical imaging of the membrane without removing the cover and exposing the contents to potential contamination.

Claims 62-64 lack an inventive step under PCT Article 33(3) as being obvious over Freiburghaus in view of Li et al. The reference of Freiburghaus has been discussed above. While the reference discloses a porous analyte bead, the reference is silent as to the method of making the bead. The reference of Li et al. discloses a conventional method for forming porous gel beads that includes forming an emulsion and controlling the temperature of the emulsion to form porous polymer beads. In view of this teaching, it would have been obvious to one of ordinary skill in the art at the time the invention was made to employ the method of Li et al. to form the beads of the primary reference for the known and expected result of employing an art recognized means for forming a porous polymer bead.

Claims 65-68, 70 and 71 lack an inventive step under PCT Article 33(3) as being obvious over Freiburghaus in view of Kambra et al. The reference of Freiburghaus has been discussed above. While the reference of Freiburghaus discloses the use of analyte particles, the reference is silent as to the method and device recited in claims 65-68, 70 and 71 above. The reference of Kambra et al. discloses that it is known in the art to employ probe particles in a flow and capture system that optically images the analyte particles. In view of this teaching, it would have been obvious to one of ordinary skill in the art at the time the invention was made to employ the

**Supplemental Box**
(To be used when the space in any of the preceding boxes is not sufficient)

analyte particles in the system of the reference of Kambra et al. for the known and expected result of providing art recognized analyte beads in an art recognized system for handling the beads, contacting the beads with sample and optically determining the presence of a desired analyte associated with the beads.

Claims 50-55 and 69 meet the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest using a plurality of wavelengths and/or masks as recited in the above claims to form an image of the collected material on a collection membrane.

Claims 1-72 meet the criteria set out in PCT Article 33(4), and thus have industrial applicability because the subject matter claimed can be made or used in industry.

Serial No. 09/775,343 entitled "Portable Sensor Array System"; and U.S. Patent Application Serial No. 10/072,800 entitled "Method and Apparatus for the Confinement of Materials in a Micromachined Chemical Sensor Array".

**Method of Testing for Microbes Using A Membrane System**

In another embodiment, a membrane based flow sensor was prepared which is configured to accommodate the capture of microbes with a filter placed within the fluidics device. Microbes, whose size is larger than the pores of the filter, are captured in the flow cell assembly. The captured microbes may be analyzed directly or may be treated with visualization compounds.

A variety of microbes may be captured and analyzed using a membrane based flow sensor as described herein. As used herein, "microbe" refers to any microorganism, including but not limited to, a bacteria, spore, protozoan, yeast, virus, and algae. Some microbes that are of particular interested for detection include a variety of toxic bacteria. Examples of bacteria that may be detected using a membrane based flow sensor include, but are not limited to *Escherichia coli O157:H7, Cryptosporidium, Vibrio cholerae, Shigella, Legionnella, Lysteria, Bacillus globigii,* and *Bacillus anthracis* (anthrax). Viruses may also be detected using a membrane.

Shown in FIG. 1 is an exploded view of a membrane based flow sensor 100. Flow sensor 100 includes a membrane 110 that is sandwiched between at least two members 140 and 150. Members 140 and 150 are configured to allow fluid to flow to and through membrane 110. Members 140 and 150 are also configured to allow detection of analytes, after the analytes have been captured on membrane 110. A variety of different materials may be used for membrane 110, including, but not limited to, Nuclepore ® track-etched membranes, nitrocellulose, nylon, and cellulose acetate. Generally, the material used for membrane 110 should have resistance to non-specific binding of antibodies and stains used during the visualization and detection processes. Additionally, membrane 110 is composed of a material that is inert to a variety of reagents, buffers, and solvents. Membrane 110 may include a plurality of sub-micron pores that are fairly

After the bead library has been optimized for the indicator, the beads that have been collected represent a reduced population of the originally produced beads. If the population of beads is too large, additional screening may be done by raising the intensity threshold. Now that the beads that exhibit optimal interaction with a receptor have been identified, the remaining beads are optimized for displacement of the indicator by the analyte of interest. Thus, the remaining beads are treated with a fluid that includes the analyte of interested, as depicted in FIG. 11C. The analyte is represented by the circle. For some beads, the analyte will cause displacement of the indicator, causing the color or fluorescence of the bead to be reduced, as depicted in FIG. 11D. The intensity of the color or fluorescence of the bead after it interacts with an analyte will be based on how the competitive displacement of the indicator. A bead that exhibits weak or no color or fluorescence when treated with an analyte is the most desirable. Such beads show that the analyte is readily bound by the receptor and can readily displace the indicator from the receptor.

Once again a flow cytometer may be used to determine the optimal beads for use in an assay. A library of beads that have been optimized for interaction with an indicator are treated with a fluid that includes an analyte. The treated beads are passed through a flow cytometer and the beads are separated based on intensity of color or fluorescence. The beads that exhibit a color or fluorescence below a predetermined intensity are collected, while beads that show a color or fluorescence above the predetermined intensity are sent to a waste collection. The collected beads represent the optimal beads for use with the selected analyte and indicator. The identity of the receptor coupled to the bead may be determined using known techniques. After the receptor is identified, the bead may be reproduced and used for analysis of samples.

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AMENDED SHEET

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forming a plurality of particles, wherein each particle comprises a receptor coupled to a polymeric resin, wherein a plurality of different receptors are coupled to the particles;

interacting the plurality of particles with an analyte;

determining which particles interact with the analyte and the extent to which the interact with the analyte;

separating particles that interact with the analyte and meet a predetermined criteria from particles that do not substantially interact with the analyte or do not meet a predetermined criteria;

adding the separated particles that interact with the analyte and meet the predetermined criteria to a sensor array.

71. The method of claim 70, wherein separating the particles comprises separating the particles using a flow cytometer.

72. An analyte detection device comprising:

a body;

a porous membrane coupled to the body.